

Regeneration Research NEWSLETTER



The Twelfth International Symposium on Neural Regeneration

The Twelfth International Symposium on Neural Regeneration (ISNR) was held at the Asilomar Conference Center in Pacific Grove, California from December 5-9, 2007. The meeting was co-sponsored by the U.S. Department of Veterans Affairs (Biological Laboratory Research and Development and Rehabilitation Research and Development Service), the Paralyzed Veterans of America (Spinal Cord Research Foundation), the National Institutes of Health (National Institute of Neurological Disorders and Stroke, and Office of Rare Diseases), the Christopher and Dana Reeve Foundation and the United Spinal Association. Additionally, a generous donation was received from the Shapiro Spinal Cord Research Foundation.

The Symposium was organized by Dr. Roger Madison (Symposium Director, VA Medical Center and Duke University, Durham, NC), and the program planning committee which included Drs. David Gardiner (University of California, Irvine), Jane Lebkowski (Geron Corporation), Michael Sofroniew (University of California, Los Angeles) and John Steeves (International Collaboration on Repair

Discoveries/University of British Columbia). Guest attendees representing co-sponsoring institutions at the planning meeting were Drs. Vivian Beyda (United Spinal Association) and Naomi Kleitman (NIH-NINDS).

The keynote speaker for this year's symposium was Stephen Waxman from Yale Medical School. Featured talks were given by Melitta Schachner from Universitat Hamburg and Rutgers University, Douglas Kerr from Johns Hopkins University School of Medicine, Steven Cramer from the University of California - Irvine, Douglas Wallace from the University of California - Irvine and Michael Fehlings from the University of Toronto.

ISNR Staff

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The Director's Chair

From the Office of the International Symposium
on Neural Regeneration

Roger D. Madison, Ph.D. - Director



2007 Highlights

The International Symposium on Neural Regeneration celebrated another successful gathering at the 2007 conference which was attended by 216 participants, including 66 students, with a total of 91 posters being presented. All of the symposium events were of great interest to the participants with the debate and trainee awards drawing the most interest.

The debate session of the symposium was another successful event. The focus was "Growth Across the Glial Scar Will Be Sufficient for Functional Recovery" and was again chaired by Keith Crutcher (University of Cincinnati). James Fawcett (University of Cambridge), Paul Reier (University of Florida) and Jerry Silver (Case Western Reserve University) along with Jeffery Kocsis (Yale University), Edward Hall (University of Kentucky) and Oswald Steward (University of California - Irvine) participated. The debate session had the highest attendance of any session at the symposium. The format included a group presentation of each side's argument followed by a rebuttal period. The debate sparked much conversation throughout the remainder of the symposium. (Pictured at left are members of the 2007 ISNR Debate Teams - L to R are James Fawcett, Paul Reier, Jerry Silver, Keith Crutcher, Jeff Kocsis, Ed Hall and Os Steward)



The Frederick Seil Trainee Award, which was established in 2003 to honor the first director and founder of ISNR, was awarded for 2007 to Angela Scott and Lesley Soril, both representing the University of British Columbia and International Collaboration on Repair Discoveries (ICORD). Each received a \$250 cash award, and their names have been engraved on the Frederick Seil Trainee Award perpetual plaque. As an added bonus, Dr. Seil was in attendance at the meeting and personally presented the awards. Additional poster awards were presented by Dr. Vivian Beyda of the United Spinal Association to recognize Ward Plunet (UBC/ICORD), Jacquelyn Cragg (UBC/ICORD), Qin Chen (Baylor), Joe Bonner (Drexel University) and Jennifer Wong (UBC/ICORD). The United Spinal Association generously provided a \$50 cash award and a certificate for each of these winners. All awards were chosen by planning board members who reviewed the poster sessions.



Lesley Soril and Angela Scott

In addition to these poster awards, two individuals were selected to give platform presentations based on the abstracts they submitted. Michael Shifman of the University of Pennsylvania and Allan Bieber of the Mayo Clinic were chosen to give these talks in the final "Emerging Topics" conference session. ISNR congratulates all of these winners.

Following the format of preceding neural regeneration symposia, the program was divided into six sessions, which included: 1) Intrinsic Mechanisms of Regeneration, chaired by Herbert Geller; 2) MR Imaging of Spinal Cord Injury and Repair, chaired by Patrick Stroman; 3) Role of Training, Synaptic Plasticity and Learning on Functional Recovery, chaired by Fernando Gomez-Pinilla; 4) Growth Across the Glial Scar Will Be Sufficient for Functional Recovery (debate), chaired by Keith Crutcher; 5) Human Stem Cells for Model Development and Repair: Opportunities and Challenges, chaired by Arlene Chiu; and 6) Emerging Topics/Clinical Updates, chaired by Naomi Kleitman. Brief summaries of the keynote and featured speakers presentations are given below followed by a listing of session chairmen and speakers.

Men on Wheels, Men on Fire: Sodium Channels as Molecular Targets in Disorders of the Spinal Cord (Stephen Waxman, Yale Medical School)



Dr. Waxman began his keynote address by stating that voltage-gated sodium channels are widely expressed within neurons and play pivotal roles in neuronal signaling. Although neurophysiology classically referred to "the" sodium channel as if it were a singular entity, it is now known that ten different genes encode ten different isoforms of sodium channels, with different kinetic and voltage-dependent properties. It is thus not surprising that sodium channels can play multiple roles in neuronal pathophysiology. Dr. Waxman described the human hereditary pain disorder (erythromelalgia, the "man on fire syndrome") which is due to a gain-of-function mutation in a sodium channel that makes nociceptive DRG neurons hyperexcitable, thus providing a model in humans of chronic pain due to sodium channel dysfunction. Conversely, changes in the expression of sodium channels can play an adaptive role in some demyelinated

axons, and thus may provide a molecular substrate for clinical remissions in disorders such as multiple sclerosis (MS). Dr. Waxman concluded by discussing the complexity of the path from laboratory bench to clinic.

Recognition Molecules and Neural Repair (Melitta Schachner, Universitat Hamburg/Rutgers University)



Dr. Schachner's presentation included recent work highlighting both the beneficial and adverse impacts of immunoglobulin superfamily adhesion molecules and extracellular matrix glycoproteins on regeneration after spinal cord injury in the adult mouse. Overexpression of the immunoglobulin superfamily adhesion molecule L1 by embryonic stem cells or application of adeno-associated virus encoding for L1 promoted functional recovery, while CHL1 was adverse to regeneration. Adhesion molecule-associated carbohydrates, such as the human natural killer cell antigen 1 (HNK-1) and the neural cell adhesion molecule NCAM associated polysialic acid enhanced regeneration in the central and peripheral nervous system of adult mice. Dr. Schachner concluded by stressing that combinatorial approaches in targeting will be important for future therapy.

Stem Cells and Spinal Cord Disorders: Models of Disease and Therapeutic Strategies (Douglas Kerr, Johns Hopkins University School of Medicine)



Dr. Kerr's presentation reviewed recent work with several stem cell-based therapies for multiple sclerosis (MS), transverse myelitis (TM) and spinal muscular atrophy (SMA). He presented promising data using high-dose cyclophosphamide (Revimmune) as a one-time front-loaded therapy to induce long term remission in patients with MS. In preliminary work with 10 patients there

was a 90% reduction in gadolinium enhancement by 18 months, a 95% reduction in exacerbation frequency and a 45% reduction in disability. Dr. Kerr also reported on preclinical studies using glial restricted precursors (GRPs) as potential therapeutic agents for CNS demyelinating disorders, with the goal of initiating a single center, open label pilot study with dose escalation to obtain preliminary data on the safety and tolerability of GRP cells in patients with disability from TM. He closed with reviewing the ability of embryonic stem cell-derived motor neurons to functionally replace those destroyed in paralyzed adult rats, and the need to replicate such findings in large mammals with the eventual goal of initiating a clinical trial of ES cell-derived motor neurons to reconstitute motor neurons damaged in infants with the fatal motor neuron disorder SMA.

Recovery from Stroke (Steven Cramer, University of California - Irvine)



Dr. Cramer reviewed that patients show spontaneous behavioral recovery during the weeks that follow a stroke, though this is generally incomplete. Possible mechanisms underlying such recovery

include angiogenesis, synaptogenesis, and qualitative/quantitative changes in neurons and glia. This has led to an interest in restorative therapies which aim to improve outcome not by salvaging tissue but instead by enhancing repair of surviving elements, including: use of small molecules, growth factors, cell-based therapies, electromagnetic stimulation, neuroprosthetics, motor imagery, intensive training, and robotic devices.

Mitochondrial Etiology Of Aging And Age-Related Neurodegenerative Disease (Douglas Wallace, University of California - Irvine)



Dr. Wallace (aka Mr. Mitochondria) discussed various genetic aspects of both the nucleo-cytosol and mitochondria. Inherited pathogenic mitochondrial DNA (mtDNA) muta-

tions have been linked to a wide range of metabolic and degenerative diseases, and somatic mtDNA mutations accumulate with age in a broad spectrum of organisms. Introduction of catalase into the mouse mitochondrial matrix reduces the mtDNA somatic mutation rate and extends life span, and treating short-lived *Drosophila* mutants with mitochondrially-targeted antioxidants can restore the life span. Ancient adaptive mtDNA polymorphisms have been associated with altered risk for metabolic and neurodegenerative diseases, such as metabolic syndrome and Parkinson disease, and somatic mtDNA mutations are elevated in the brains of Alzheimer Disease patients and Down Syndrome patients with dementia. Finally, both germline and somatic mtDNA mutations are associated with various cancers including prostate cancer. Dr. Wallace stressed therefore that diseases which appear "complex" when viewed exclusively from the nucleo-cytosol perspective might be more readily understood if the contribution of the mitochondrial organism were also considered.

Repair and Regeneration of the Injured Spinal Cord: Opportunities for Clinical Translation of Basic Research Discoveries (Michael Fehlings, University of Toronto)



Dr. Fehlings reviewed recent clinical trials related to SCI, including: the STASCIS trial examining the impact of early surgical decompression; a planned clinical trial which will evaluate the neuropro-

protective efficacy of the sodium/glutamate antagonist riluzole; and the Cethrin trial of a recombinant Rho inhibitor to reduce cell death and enhance neural regeneration. He also reviewed late-stage preclinical studies focusing on neural stem cell based remyelination strategies.

Intrinsic Mechanisms of Regeneration (Chaired by Herbert Geller, NIH/NHLBI)

Paul Bridgman (Washington University) presented "Understanding Mechanisms of Axon Guidance: How Growth Cones Steer". Frank Gertler (Massachusetts Institute of Technology)

presented "Role of Cytoskeletal Dynamics During Neurite Initiation and Outgrowth". Adriana Di Polo (University of Montreal) presented "The Long and Winding Road: Axon Regeneration Within the Optic Nerve". Joseph Fetcho (Cornell University) presented "Imaging Regeneration In Vivo".

Noninvasive MR Imaging of Spinal Cord Injury and Repair (Chaired by Patrick Stroman, Queen's University)

Eric Schwartz (University of Pittsburgh Medical Center) presented "Diffusion Tensor MRI (DTI) and the Evaluation of Axonal Integrity Following Spinal Cord Injury". Thomas Mareci (University of Florida) presented "The Resolution of Complex Spinal Cord and Brain Structures In Vivo and Ex Vivo Using High Angular Resolution Diffusion MRI". Adam Flanders (Thomas Jefferson University) presented "Clinical Utility of MRI in Spinal Cord Injury: Correlation With Clinical Deficit and Recovery".

Role of Training, Synaptic Plasticity and Learning on Functional Recovery (Chaired by Fernando Gomez-Pinilla, University of California - Los Angeles)

Dr. Gomez-Pinilla presented "The Influences of Diet and Exercise on Plasticity and Repair". Jeffrey Kleim (Malcolm Randall VAMC/University of Florida) presented "The Utility of Adjuvant Therapies to Enhance Cortical Plasticity and Recovery from Stroke". V. Reggie Edgerton (University of California - Los Angeles) presented "Can Locomotion Be Controlled by Peripheral Afferents After a Complete Spinal Cord Injury?"

DEBATE: Growth Across the Glial Scar Will Be Sufficient for Functional Recovery (Chaired by Keith Crutcher, University of Cincinnati Medical Center)

James A. Fawcett (University of Cambridge), Paul J. Reier (University of Florida) and Jerry Silver (Case Western Reserve University) presented a position of "YES" for the statement. While Jeffery D. Kocsis (Yale University School of Medicine), Edward Hall

(University of Kentucky College of Medicine) and Oswald Steward (University of California - Irvine) presented a position of "NO" for the statement.

Human Stem Cells for Model Development and Repair: Opportunities and Challenges (Chaired by Arlene Chiu, California Institute for Regenerative Medicine)

Hans Keirstead (University of California - Irvine) presented "hESC-Derived Cell Populations for the Treatment of Spinal Cord Injury". Su-Chun Zhang (University of Wisconsin) presented "Neural Subtype Specification of Human ESCs: Model for Neural Development and Source for Brain Repair". Lorenz Studer (Sloan-Kettering Institute) presented "Human ES Cells in Development and Neural Repair". Curt Freed (University of Colorado Health Sciences) presented "Converting Human Embryonic Stem Cells to Dopamine Neurons for the Treatment of Parkinson's Disease".

Emerging Topic/Clinical Trials (Chaired by Naomi Kleitman, NIH/NINDS)

Michael Shifman (University of Pennsylvania) was selected to present "Dependence Receptors And Retrograde Neuronal Death After Spinal Cord Injury" and Allan Bieber (Mayo Clinic) was selected to present "Genetic Determinants of Cns Repair Following Chronic Demyelination In Mice". Grace Griesbach (University of California - Los Angeles) presented "Optimizing the implementation of exercise for the treatment of traumatic brain injury". Corey McCann (Harvard University) presented "Retrograde maintenance of synaptic connections in vivo".

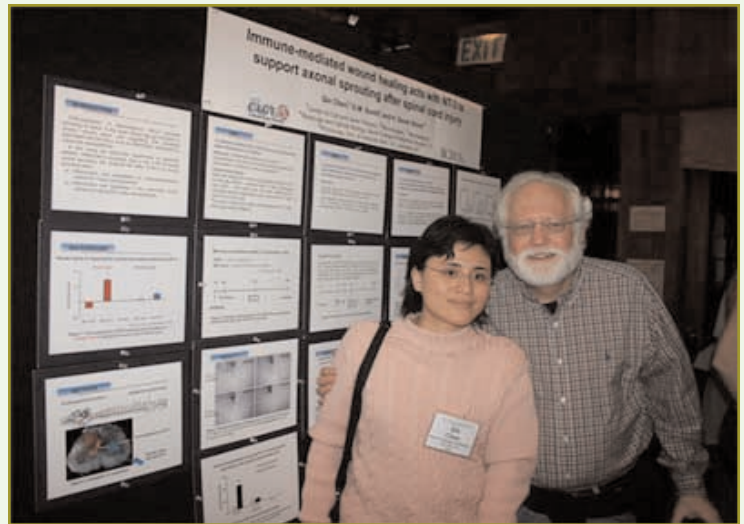
In addition to the platform presentations, free communications were presented in the form of 91 posters. Posters were displayed in two sessions. Abstracts of both speaker and poster presentations were published for the program booklet as part of the November/December 2007 issue of *Neurorehabilitation and Neural Repair*, Ed. Bruce Dobkin (Volume 21, Number 6, Pages 576-617).

ISNR

2007



Arlene Chiu



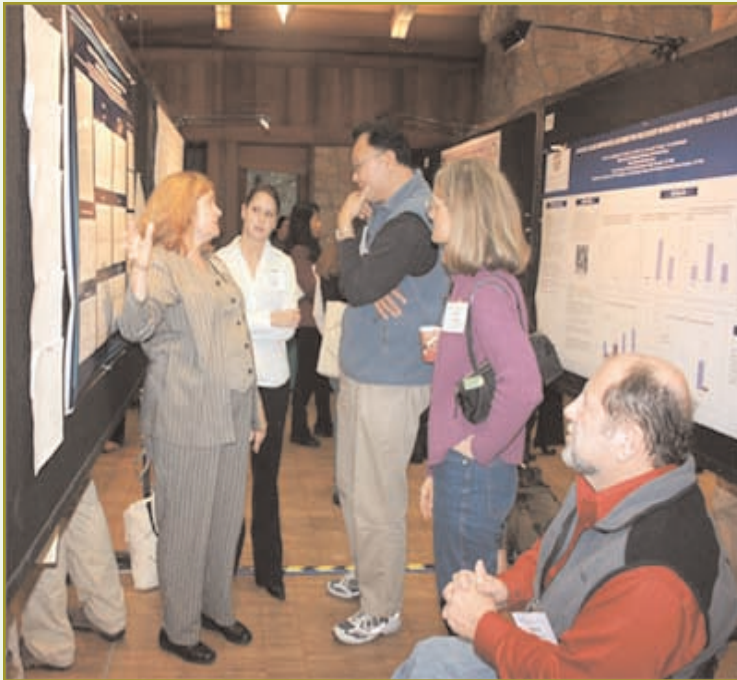
David Shine and Qin Chen



2007 Poster Award Winners

Front row - L to R- Dr. Vivian Beyda (United Spinal Association), Qin Chen, Jennifer Wong, Lesley Soril, Jacquelyn Cragg, Dr. Roger Madison and Dr. Fredrick Seil. Back row - L to R - Joe Bonner, Ward Plunet and Angela Scott

ISNR *2007*



Poster Session



Michael Selzer



Matt Ramer and Sasha Rabchevsky

The ISNR Story

The office of the International Symposium on Neural Regeneration was asked by United Spinal Association to summarize the history of ISNR. As the symposium has passed a twenty year milestone, the ISNR office would like to take this opportunity to reflect on the history of the symposium and pay tribute to some of the many individuals who have influenced the ongoing success of this very important meeting.

The ISNR is a biennial symposium series where the primary purpose is to present current work in neural regeneration, especially in those areas of research in which there has been some notable recent progress or in which some particularly interesting issues have been raised. A secondary purpose is to foster an atmosphere that is both stimulating and conducive to a free interchange of ideas among investigators, or between seasoned investigators and students. The target audience of the symposium is a mixture of faculty, physicians, students, and laboratory staff brought together in a forum to discuss strategies for discovering methods of recovery from injury or dysfunction of the nervous system. To the spinal cord research community, the significance of the ISNR meeting is that it provides a format for both formal and informal exchanges of ideas on research in neural regeneration. For individuals with spinal cord dysfunction, meetings like this encourage new ideas, new research approaches, new collaborations and new projects, the products of which bring the possibility of functional recovery ever closer to realization. The ISNR symposia have become established, regularly occurring events with high attendance by both students as well as internationally recognized experts in the field of neural regeneration.

The symposium series began in 1985 under the directorship of Dr. Fredrick Seil through the Office of Regeneration Research Programs within the Veterans Affairs Medical Center (VAMC) in Portland, Oregon. The ISNR meetings have been held every other year since that initial meeting in 1985. Upon Dr. Seil's retirement in 2001, the organizational responsibilities of the symposium were passed to the current director, Dr. Roger Madison of the Veterans Affairs Medical Center and Duke University in Durham, North Carolina. Dr. Madison works with a planning board, comprised of specialists in the field of regeneration research along with representatives of the sponsoring organizations, to plan for each conference. Through the past guidance of Dr. Seil and present leadership of Dr. Madison, the expertise of a scientific advisory board and the ongoing commitment of sponsoring organizations, the symposium has passed a twenty year milestone and continues to grow and become more popular with every event.

Financial support for the meetings initially came from the Department of Veterans Affairs (VA) and the Paralyzed Veterans of America (PVA). Very quickly the National Institutes of Health (NIH) recognized the importance of the ISNR meetings and began to offer their support beginning in 1987 (and continuing for every meeting since then). Several other foundations began offering support for the meetings such that by 1993 the meeting was being supported by the VA, the NIH, the PVA, the American Paralysis Association (presently the Christopher and Dana Reeve Foundation), and the Eastern Paralyzed Veterans of America (presently United Spinal Association). In addition, generous support has been received from individual donors on a non-recurrent basis. All of ISNR's sponsoring organizations recognized the long-term commitment that is needed to advance spinal cord injuries and disorders (SCI/D) research efforts. Support is gratefully acknowledged for all aspects of the symposium from travel and accommodations of staff and invited participants to travel awards and poster awards for students. The latter is especially important in terms of encouraging students and new researchers entering the field. This commitment to the next generation of research scientists has significantly contributed to the success of the ISNR.

The symposium organizers arranged for the first meeting to be held at the Asilomar Conference Center in Pacific Grove, California, a California State Park. Subsequent meetings continue to be held at Asilomar as the facility provides appropriate access for wheelchair participants and offers a relaxing atmosphere for discussion and collaboration. With the tranquil setting in mind, the meeting is organized with a single session format to allow participants the opportunity to participate in each session. The symposium boasts a committed following of participants and continues to attract new students and researchers year after year. Many of the participants who attended their first ISNR meetings as students have returned to more recent meetings as speakers, indicating the long-term impact that the ISNR meetings have had on these highly recognized international experts in the SCI/D research field.

For students, this meeting provides an opportunity to interact directly with leading scientists in the field. Students comprise approximately 30% of the participants at this meeting and they have a significant contribution to the interaction among the overall participant population. In addition to the travel awards which make it possible for many of the students to attend the meeting, 2003 marked the introduction of poster awards to honor the longtime commitment of Dr. Fredrick Seil and to recognize the outstanding achievements in research by the students. These poster awards have become highly coveted by the student participants.

The long-range plan of this event is to continue to hold these symposia on alternate years at the same site, and to vary the programs of successive symposia, so that coverage of the broad field of neural regeneration research over a period of years will be as extensive as possible. The Thirteenth International Symposium on Neural Regeneration is planned for December 9 through 13, 2009 at the Asilomar Conference Center in Pacific Grove, California. The continued success of this symposium series is largely dependent on the ongoing support by each of the participating organizations. Each organization makes it possible to encourage and support the participation of students and leaders in the field of regeneration research to attend this meeting year after year.

For more information about the International Symposium on Neural Regeneration, please contact:

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or visit our website:

<http://www.rehab.research.va.gov/Neural/neural.htm>

Looking Ahead To ISNR 2009

Symposium Session Proposals

If your favorite topic has not recently been presented at one of the international symposia, we encourage you to submit a proposal for a symposium session. The program planning committee is meeting on September 19-21, 2008, to formulate the program for the Thirteenth International Symposium on Neural Regeneration (ISNR) scheduled for December 2009. Proposals may be received in the ISNR Office as late as September 1, 2008 and still be considered, but earlier submission is recommended for advance distribution to committee members. Proposals will not be considered, however, if they are not submitted in an appropriate format (see guidelines below).

Submission Guidelines

Symposium sessions are chosen for their timeliness, current interest and recent progress. One of the goals of these symposia is to cover the field of neural regeneration as broadly as possible. This cannot be done in a single year, and therefore an attempt is made to vary the programs in successive symposia so that eventually the spectrum of neural regeneration research is covered. A symposium session proposal should define a session topic and include a few words about why the topic should be presented. A chairman should be identified (often the symposium proposer), along with four or six first choice speakers. Information on the speakers should include institutional affiliation, address, telephone number (if available), and a few words on what area this speaker would cover. In addition, at least one (preferably more) alternate should be listed for each speaker or chairman, along with institutional affiliation and other identifying data, as the first choice speaker is not always available because of some conflict. Potential speakers should not be contacted in advance, as invitations are issued by the Director's office if the program planning committee accepts the session. Some thought should also be given to whether a potential speaker has previously been a recent symposium presenter, as an attempt is made to vary the individuals participating in the program. Lists of speakers in past symposia are available from the ISNR office and are also posted on our web site: <http://www.rehab.research.va.gov/Neural/neural.html>.

Please submit session proposals via email to:

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